76 (amended). The protein of claim [73 which has a Val residue at said position 239] 74 in which the Met residue at position 239 is substituted by Val.

Please add the following new claims:

77. The protein of claim 24, which is a human E5-1 protein.

78. The protein of claim 71, wherein said mutant protein is naturally occurring.

79. The protein of claim 77, which is a splice variant of said human E5-1 protein.

REMARKS

The specification has been amended to correct minor typographical and clerical errors, to maintain consistent terminology, to update the status of the parent applications, and to conform with the requirements set forth in 37 C.F.R. § 1.821 *et seq.* A computer readable form of the Sequence Listing filed herewith is also attached. The content of the paper and computer readable copies are the same. 37 C.F.R. § 1.821(f). No new matter has been added.

Claims 25 and 72 have been canceled. Claims 24, 71 and 73-76 have been amended in response to the objections raised under 35 U.S.C. §§ 112 and 132. Claim 24 is directed to a substantially pure mammalian E5-1 protein, support for which is set forth, e.g., on pages 12, line 12 through page 13, line 1 and pages 27-31. New dependent claim 77 is directed to a human E5-1 protein, support for which is set forth, e.g., on pages 12, line 12 through page 13, line 1 and pages 27-31. New dependent claim 78 is directed to naturally occurring mutant E5-1 proteins, support for which is set forth, e.g., on page 12, line 24 through

page 13, line 1 and pages 30-31. New dependent claim 79 is directed to splice variants of the human E5-1 protein, support for which is set forth, e.g., on page 12, line 19 through page 13, line 1, and page 29, lines 25-30. Accordingly, no new matter has been added. Entry of the Amendment is therefore respectfully requested.

The Objections

On page 2 of the Office Action, the Examiner has objected to the Sequence Listing for failing to identify several sequences disclosed on pages 48 and 66 and in Tables 3, 5 and 8 of the specification. The Examiner has also objected to certain references to the SEQ ID NOS. in the specification because several of the sequences identified therein do not correspond to the SEQ ID NOS. listed in the amended Sequence Listing filed on February 27, 1996.

Applicants have enclosed an amended Sequence Listing and corresponding diskette, which include the nucleotide and amino acid sequences identified by the Examiner, as well as additional sequences disclosed in the original specification that did not have corresponding SEQ ID NOS. The enclosed Sequence Listing addresses the other errors as well. Accordingly, withdrawal of the objections are requested.

On page 3 of the Office Action, the Examiner has objected to the Amendment filed on February 29, 1996 under 35 U.S.C. § 132, as introducing new matter. The Examiner contends that the Amendment added a Sequence Listing that does not correspond to the original sequences disclosed on pages 76-164 of the original specification.

Applicants have carefully reviewed the specification, enclosed a new Sequence Listing herein, and amended the specification accordingly. No new matter has been added. As such, Applicants submit that the SEQ ID NOS. referenced in the specification as amended now correspond to the SEQ ID NOS. identified in the Sequence Listing filed herewith. Withdrawal of the new matter objection is respectfully requested.

The Rejections

Claims 24-25, 71-72 and 74-76 have been rejected under 35 U.S.C. § 112, first paragraph, as non-enabled for claims directed to all E5-1 proteins on the ground that the specification fails to disclose a specific use for the purified E5-1 protein, variants, or muteins thereof except for E5-1 proteins having the sequence of SEQ ID NO:138 (wild-type protein) and SEQ ID NO:138 wherein the Asn at amino acid position 141 has been replaced by Ile and/or wherein the Met at amino acid position 239 has been replaced by Val (i.e., the naturally occurring mutants).

Applicants traverse this rejection. The specification discloses the normal and mutant mammalian E5-1 proteins of the present invention. The specification teaches that disease mechanism insights and therapies analogous to those described in relation to the ARMP gene are available as a result of the identification and isolation of the E5-1 genes and proteins. *See, inter alia*, page 12, line 12 through page 13, line 1, page 13, line 11 through page 14, line 26, and pages 49-54. The cases cited by the Examiner are not on point, because the facts involved claims directed to DNA sequences. Applicants' claims are directed to proteins. Nonetheless, it is clear that

Applicants were the first to discover the E5-1 gene and its corresponding amino acid sequence. Moreover, Applicants teach how to identify other proteins without undue experimentation. See, e.g., page 34, lines 3-23. One reading the instant specification would certainly recognize that Applicants were in possession of the presently claimed invention. See, e.g., pages 5, 12-13 and 27-31. Withdrawal of this rejection is respectfully requested.

Claims 72 and 74-76 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite on numerous grounds, namely: claim 72 lists amino acid positions for mutations in the absence of any reference to a specific sequence; claim 74 recites specific mutations with respect to SEQ ID NO:138, but dependent claim 71 is not limited to the protein of SEQ ID NO:138, and therefore is confusing; and claim 76 is confusing in its dependency on claim 73 rather than claim 74.

These claims have been amended so as to avoid any potential confusion with respect to amino acid positions and dependency. Withdrawal of this rejection is requested.

Claims 24-25 and 71 have been rejected under 35 U.S.C. § 103 as being obvious over L'Hernault *et al.* The Examiner has concluded that the SPE-4 protein from *C. elegans* disclosed by meets the limitations of the claims, because the specification fails to define the metes and bounds of an E5-1 protein.

Applicants traverse the rejection because *L'Hernault* does not disclose or suggest mammalian E5-1 proteins. *C. elegans* is a non-mammalian species. Withdrawal of this rejection is requested.

On page 9 of the Office Action, the Examiner has requested Applicants to advise the Office of all co-pending applications claiming subject matter related to E5-1 proteins. The Examiner's attention is directed to U.S. Patent Application Serial No. 08/967,101, filed November 10, 1997, which claims polynucleotides encoding E5-1 (now conventionally referred to in the art as presenilin II or "PS2") proteins.

Applicants submit that the present Amendment serves to overcome all outstanding objections and rejections and places the pending claims in condition for allowance. An early Notice to this effect is earnestly solicited. The Examiner is invited to contact the undersigned if she has any questions.

Respectfully submitted,

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